

BEFORE

THE UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

INITIAL COMMENTS OF THE

AMERICAN HERBAL PRODUCTS ASSOCIATION

ON THE FOOD AND DRUG ADMINISTRATION'S REQUEST FOR COMMENT ON
DRAFT GUIDANCE:

**“GUIDANCE FOR INDUSTRY: SUBSTANTIATION FOR DIETARY SUPPLEMENT
CLAIMS MADE UNDER SECTION 403(r)(6) OF THE FEDERAL FOOD, DRUG
AND COSMETIC ACT”**

January 10, 2005

2004D-0466

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The American Herbal Products Association ("AHPA") is the national trade association and voice of the herbal products industry, comprised of companies doing business as growers, processors, manufacturers, and marketers of herbs and herbal products. AHPA serves its members by promoting the responsible commerce of products that contain herbs.

In reviewing the Food and Drug Administration's ("FDA's" or "the Agency's") draft guidance on substantiation for dietary supplement claims which is the subject of these comments, AHPA and its members note and are alarmed by the fact that the Agency has given almost no attention whatsoever to the value of information about the traditional uses of botanicals to substantiate claims for dietary supplements that contain traditionally used herbs and herbal ingredients. AHPA will show in these comments that the Agency has departed substantially from the manner by which the Federal Trade Commission ("FTC") has determined to assess substantiation for traditional use claims for dietary supplements. AHPA will also show that, despite its prior endorsement of substantiation principles and recommendations for traditional use claims that were made by the Commission on Dietary Supplement Labels, the Agency has in this draft guidance departed from those principles without any explanation whatsoever. In addition, AHPA will provide examples of contemporary regulatory schemes in Canada, Australia and the European Union, where clear guidance has been established for substantiating traditional use claims with information from historical sources that discuss and describe the traditional uses of herbs.

Background

Under section 403(r)(6) of the Federal Food, Drug and Cosmetic Act ("the Act") as amended by the Dietary Supplement Health and Education Act of 1994 ("DSHEA"), marketers of dietary supplements are required to have substantiation that claims made for their products related to nutritional deficiency, structure/function, or general well-being are truthful and not misleading. When such claims are made, DSHEA requires that the claim be footnoted with the following disclaimer:

“This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”

In a Federal Register notice of November 9, 2004 the Agency announced the availability of a draft guidance titled *Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug and Cosmetic Act* (the “Draft Guidance”). The Agency stated that the Draft Guidance is being issued as a Level 1 guidance consistent with FDA’s good guidance practices, and that the Draft Guidance describes the amount, type, and quality of evidence that FDA recommends a manufacturer have to substantiate a claim under section 403(r)(6) of the Act (hereinafter “structure/function claim” or “dietary supplement claim”). In addition, the Agency stated that it intends to apply a standard for substantiating dietary supplements claims that is consistent with the FTC’s standard of “competent and reliable scientific evidence.”

In conformity with its obligation under the Paperwork Reduction Act of 1995 (“PRA”), the Agency also provided estimates of the burden of the proposed collection of information related to dietary supplements claims.

The Agency requested that comments to the Draft Guidance and to the Agency’s PRA estimates be submitted by January 10, 2005.

FDA’s Draft Guidance

In the Draft Guidance FDA observes that, although marketers of dietary supplements are held to a statutory requirement to have substantiation that dietary supplement claims are truthful and not misleading, there is no statutory definition of the word “substantiation.” The Agency also states that, in preparing the Draft Guidance, it drew upon the following:

- Its own experience with respect to the regulation and case law regarding substantiation of various statements that may be made in labeling of dietary supplements, conventional foods, and drug products;
- The FTC’s experience with its policy on substantiating claims made for dietary supplements; FDA further states that the Draft Guidance “is

modeled on, and complements” the FTC Advertising Guide¹ published in 2001;

- Recommendations from the Commission on Dietary Supplement Labels, and specifically, the recommendations on pages 42-45 of that Commission’s Final Report².

FDA also states that the FTC has typically applied a substantiation standard of “competent and reliable evidence” to dietary supplement claims, and that “FDA intends to apply a standard for the substantiation of dietary supplement claims that is consistent with the FTC approach.” In discussing what the FTC substantiation standard is, FDA cites the FDA Advertising Guide, as follows:

“...tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that have been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.”

FDA further states that it “may accord some deference to” an “existing standard for substantiation developed by a government agency or other authoritative body.” AHPA assumes that the Agency intends that such deference would extend to international as well as domestic government agencies and authoritative bodies.

The Draft Guidance provides 21 examples to illustrate various points made in the draft. AHPA notes that the Draft Guidance explicitly mentions information about the traditional use of botanical products in only one place, in Example 16. This example states:

“A botanical product label uses the claim ‘improves vitality.’ The substantiation that the firm is relying upon consists of testimonial experience it has collected from consumers and descriptions of the botanical product’s traditional use. Although the firm may have testimonial experience to back up the basic claim being made, the claimed benefit would likely not be adequately substantiated because **neither source is based on scientific**

¹ Bureau of Consumer protection, FTC. April 2001. *Dietary Supplements: An Advertising Guide for Industry*. Washington, DC: Federal Trade Commission.

² *Report of the Commission on Dietary Supplement Labels*. November 1997. Washington, DC: Commission on Dietary Supplement Labels.

evidence. If the firm wants to make a claim of this type, we recommend that it have scientific evidence that some measurable outcome(s) associated with the general conditions cited in the claim is (are) significantly improved” (emphasis added).

Thus, FDA states in this example that neither testimonial experience nor descriptions of a botanical product’s traditional use is scientific, and inferred, by recommending that additional scientific evidence be obtained, that neither testimonial experience nor descriptions of traditional use would provide competent and reliable evidence to substantiate the claim. AHPA takes no issue with respect to FDA’s inference that consumer testimonials alone do not provide competent and reliable substantiation of a dietary supplement claim. It is AHPA’s firm position, however, that documented descriptions of traditional use and reports in texts and compendia that are generally recognized by qualified experts of an herbal product’s traditional use can provide competent and reliable substantiation of a dietary supplement claim. AHPA will show that its position is consistent with positions stated by both the FTC and the Commission on Dietary Supplement Labels, both of which have similarly acknowledged that traditional or historic use has relevance in supporting a contemporary claim for a traditional use.

FTC and claims based on traditional use

In comparison to the inference in FDA’s Draft Guidance that records of traditional use do not constitute competent and reliable evidence to substantiate dietary supplement claims, the FTC has recognized that such information may, in certain circumstances, provide such evidence.

In the Advertising Guide cited above, the FTC states that one of the factors that must be considered in determining the appropriate amount and type of substantiation needed to support a claim is “the amount of substantiation that experts in the field believe is reasonable.” In discussing what it means by “experts,” FTC discloses that it “consults with experts from a wide variety of disciplines, **including those with experience in botanicals and traditional medicines**” (emphasis added). Plainly, the reason that the FTC would consult with experts in traditional medicine in the context of claims substantiation is that FTC believes that

knowledge and expertise regarding traditional use is a relevant resource with regard to substantiation of claims based on traditional use.

The FTC Advertising Guide later dispels any uncertainty as to FTC's thinking in this matter. In a section titled, "Claims Based on Traditional Use," FTC explicitly states that an option to developing "confirming scientific evidence" for claims based on historical or traditional use is to present such claims "in such a way that consumers understand that the sole basis for the claim is a history of use of the product for a particular purpose." This statement provides meaningful guidance that firms that wish to market dietary supplements with traditional use claims may need to qualify these claims.

The FTC Advertising Guide also provides information as to situations where traditional use evidence alone would be inadequate. The FTC Advertising Guide states, for example, that an advertiser "should not suggest, either directly or indirectly, that a supplement product will provide a disease benefit unless there is competent and reliable scientific evidence to substantiate that benefit." AHPA notes that claims related to disease benefits are not permitted claims under DSHEA and are regulated as drug claims.

The FTC Advertising Guide also identifies certain limitations on the usefulness of historical use for substantiating claims:

"The advertiser should also make sure that it can document the extent and manner of historical use and be careful not to overstate such use. As part of this inquiry, the advertiser should make sure that the product it is marketing is consistent with the product as traditionally administered. If there are significant differences between the traditional use product and the marketed product, in the form of administration, the formulation of ingredients, or the dose, a traditional use claim may not be appropriate."

AHPA supports this expressed caution, and agrees that a history of traditional use can only substantiate claims for that same use, and for products that are consistent with traditional products in the form of administration, formulation of ingredients, and dose. AHPA also supports the concept of providing qualifying statements, as appropriate, to avoid consumer misunderstanding of dietary supplement claims where the sole basis of the claim is a history of traditional use of a product for a particular purpose.

In summary, the plain language and teaching of the FTC Advertising Guide is that substantiation for a claim that a product has been traditionally used for a particular purpose can be satisfied with evidence of the history of such use. Except for disease claims, the FTC has said that there need not be "confirming scientific evidence" to substantiate the traditional use, so long as evidence exists that would be recognized by qualified traditional use experts to substantiate the claim that there was (or continues to be) such traditional use, and so long as consumers are fully informed. It is AHPA's position that these FTC's positions are correct and important and ought to be recognized by FDA.

Commission on Dietary Supplement Labels and traditional use claims

The Report of the Commission on Dietary Supplement Labels ("the Report") addressed numerous issues related to dietary supplements, including substantiation of claims. This Commission was established by an act of Congress, in section 12 of DSHEA. Of some relevance to these comments is the fact that DSHEA, in describing the expertise requirements of the Commission, specified that one member "have experience in pharmacognosy, medical botany, traditional herbal medicine, or other related sciences."

In addressing dietary supplement claim substantiation the Commission's Report developed guidelines on the content of substantiation files. In discussing the evidence needed to substantiate claims in instances where historical use is cited as the evidence for a claim, the Report recommended that "the composition of the product should correspond with the material for which such claims of historical use may be made." The Report advised that a claim "based solely on historical use without supporting experimental or clinical data" would need to be "carefully qualified to prevent misleading consumers," and noted that the Commissioners did not reach a consensus on what, if any, additional support would be needed to substantiate such a claim.

Of additional interest is the fact that FDA provided comments to the Commission's Report in a Federal Register notice on April 29, 1998. In commenting on the Report's guidance on substantiation files for dietary supplement claims, cited in part immediately above, FDA stated:

“The Commission Report includes guidance on what quantity and quality of evidence should be used to substantiate claims made under section 403(r)(6) of the act. The Commission Report also includes guidance on the content of substantiation files for statements made under section 403(r)(6) of the act, including the notification letter, identification of the product’s ingredients, evidence to substantiate the statements, evidence to substantiate safety, assurances that good manufacturing practices were followed, and the qualifications of the person(s) who reviewed the data on safety and efficacy. **The agency agrees with the guidance**” (emphasis added). 63 FR 23636.

Thus, FDA in 1998 expressed its agreement with the guidance provided in the Commission’s Report on the content of substantiation files. As noted above, this guidance included the recommendations cited here regarding the need for compositional consistency between historical and contemporary products when a claim for such a product is based solely on historical use, and the possible use of qualifications, if needed to prevent misleading consumers. AHPA notes that these points are consistent with the guidance provided in FTC’s Advertising Guide, and reiterates support for both of these recommendations for claims that rely solely on the historical record.

Substantiation of traditional use claims in Canada

A new regulatory scheme went into effect in Canada on January 1, 2004 for a newly defined class of goods identified as Natural Health Products (“NHPs”). Most of the herbal products that are regulated in the United States as dietary supplements are now regulated in Canada as NHPs.

One important difference between the U.S. and Canadian regulation of herbal products is that dietary supplements in the United States are a subclass of foods, whereas NHPs in Canada are a subclass of drugs. Nevertheless, issues related to substantiation of claims for such products, especially in relation to claims based on traditional use, have much in common.

In order to sell an NHP in Canada, the marketer must provide Health Canada’s Natural Health Products Directorate (NHPD) with information that includes, among other things, the product’s recommended conditions of use and evidence of the

safety, efficacy and quality of the product when it is used in accordance with the recommended conditions of use. NHPD describes this requirement as follows:

“A claim or the recommended use or purpose is a statement that indicates the intended beneficial effect of a natural health product when used in accordance with the labeled dose (i.e. the recommended dose), duration of use, and route of administration. The term ‘recommended use or purpose’ is often used interchangeably with ‘health claim’ or ‘indications for use’.”³

NHPD has developed various types of claims for NHPs, including therapeutic claims, risk reduction claims, and structure-function claims. NHPD also recognizes two categories of claims consisting of traditional use claims and non-traditional use claims, and each of these categories of claim has relevance for each of the therapeutic, risk reduction, and structure-function types of claims. In addition, claims based on traditional use are generally limited to products that are prepared by some traditional method, such as whole or powdered plant material; aqueous, ethanolic, glycerin, or vinegar extracts; etc. Importantly, and consistent with the FTC’s Advertising Guide and the recommendations of the Commission on Dietary Supplement Labels, claims for traditional use must be prefaced with qualifiers such as “traditionally used...”.

As part of this new regulation NHPD has developed, and is continuing to develop, a Compendium of Monographs for certain ingredients that are sold as NHPs.⁴ The monographs include numerous elements, such as “proper” and common names; source (e.g., for botanicals, the part of a plant); route of administration; dosage form; recommended dose; duration of use; recommended use or purpose; risk information; specifications; and non-medicinal ingredients). Lists of current monographs for botanical and non-botanical NHPs are attached here as Appendix I.

NHPD allows firms to reference a monograph listed in the Compendium in support of the safety and efficacy of the product as part of their product license

³ Natural Health Products Directorate. 2003 (updated February 16, 2004). *Evidence for Safety and Efficacy of Finished Natural Health Products*.

⁴ Natural Health Products Directorate. November 2003. *The Compendium of Monographs*. This reference also provides information about how monographs can be used to support claims for multi-ingredient products.

application. NHPD states that “there is no need to evaluate the safety and efficacy of ingredients that are already known to be safe and efficacious when used under the conditions specified in the monograph.” At the same time, use of a monograph as substantiation for a claim is limited to products that consist of the exact product that is identified in the monograph, including all of the elements described above.

In order to substantiate a traditional use claim for a NHP for which there is not a current monograph, the marketer must generally provide at least two independent references that support the conditions of use. The references must be authoritative and from a reputable source.⁵ NHPD has provided some examples of such references that it considers authoritative, and the current list of these are provided in these comments as Appendix II.

To summarize, claims for NHPs that are based on traditional use may be substantiated by citing references that record traditional use. NHPD has developed a Compendium of Monographs to record such traditional use and references for many commonly used medicinal ingredients that comprise natural health products. The information contained in authoritative references for traditional use, as well as in the monographs in NHPD’s Compendium of Monographs, is considered by the Canadian health authorities to provide sufficient substantiation to support an efficacy claim, including a traditional use claim, for the ingredient that is the subject of the monograph.

In addition, and in line with the recommendations made by the FTC and the Commission on Dietary Supplement Labels, NHPD limits the citation of traditional use as claim substantiation to products that are consistent with traditional products in the form of administration, formulation, and dose, and requires that a qualifier, such as “traditionally used...,” be included in product labeling that relies entirely on traditional substantiation. AHPA believes these are sensible and well thought out approaches, and strongly encourages FDA, consistent with the Agency’s statement that it “may accord some deference to” standards for substantiation developed by government agencies, to consider and to adopt them. In addition, AHPA

encourages FDA to review the existing monographs that have been published by NHPD and to acknowledge that these documents can serve as substantiation for dietary supplement claims, so long as a dietary supplement making such a claim is in full conformity with all elements of the monograph.

Substantiation of traditional use claims in Australia

In Australia, the Therapeutic Goods Administration regulates traditional use claims for herbal products. Such products are regulated as a class of medicines in Australia. The parameters for such claims are set forth in the Australian Therapeutic Goods Administration (TGA) Guidelines for Levels and Kinds of Evidence to Support Indications and Claims ("TGA Guidelines"). This document, included here as Attachment I, directly addresses traditional use evidence by defining traditional use and by defining the various forms of evidence that may be used to achieve a traditional use claim.

First, the TGA Complementary Medicines Evaluation Committee established a definition for traditional use which the TGA then adopted, as follows:

"Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose."

Second, the TGA established a hierarchy of "Evidence" that may be used to support a traditional use claim. This claims substantiation hierarchy appears in Table 2 on pages 15 and 16 of the TGA Guidelines. The forms of "Evidence required to support claim" relevant to these comments are "TGA-approved Pharmacopoeia," "TGA-approved Monograph" and "Three independent written histories of use in the classical or traditional medical literature." Attachment 3 to the TGA Guidelines sets out the TGA-approved Monographs and Pharmacopoeias.

⁵ Additional details of NHPD's requirements for evidence of traditional use claims can be found in the above cited document, *Evidence for Safety and Efficacy of Finished Natural Health Products*, pages 11-15.

Third, the TGA established classes of traditional use claims that differ only slightly, but importantly. A "General" claim must be supported by one form of Evidence. A "Medium" claim must be supported by two forms of Evidence. General claims are worded in the form "This traditional medicine has been traditionally used for _____," while a Medium claim is worded "this traditional medicine has been used for _____." Thus, three historical use references alone merit only a General claim while the additional recognition in a TGA-approved Monograph or Pharmacopoeia merits the stronger claim. The nature of General and Medium claims are also different. General claims may include health maintenance and nutritional support, relief of symptoms with no reference to an underlying disease and claims for traditional syndromes and actions (i.e., *shen* (kidney)). Medium claims include health enhancement, reduction of risk of disease or disorder, reduction in frequency of discrete events, aid in management of named symptoms of named diseases, or relief of symptoms of named diseases. Obviously, some of these claims would be considered drug claims under DSHEA and they are set forth here for the sake of description only.

Fourth, the TGA has established the same type of formulation principles recognized by the FTC, the Commission on Dietary Supplement Labels, and Health Canada's NHPD. The product formulation must conform to the formulation and dose of the product as traditionally used. In addition, Australia requires that the traditional use context be respected as well:

"In assessing traditional use, the context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances, and certain behavioral rules promoting healthy diets and habits are likely to apply to them. In those cases, holistic principles are usually part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered."

"In forming a claim based on traditional use, products and substances which form part of traditional therapies should identify the therapy to which they belong or the paradigm in which the therapy has been traditionally used, as well as the product description/name and

the symptom/indication/condition for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include Traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homeopathic medicine, aromatherapy and other indigenous medicines.”

AHPA agrees that the context of classic formulations and new formulations based on classic principles must be respected. AHPA urges the Agency, consistent with the Agency’s statement that it “may accord some deference to” standards for substantiation developed by government agencies, to utilize the significant efforts of the TGA to develop principles for substantiation of traditional use claims. This effort, together with those of Health Canada and the regulatory authorities of other countries, provide the Agency with a substantial windfall in the form of review, reflection, consideration and conclusion by western allopathically trained professionals of the rich and important traditional use of herbal products. And the conclusion of these reviews is consistent - there is a substantial respect for properly formulated and documented traditional use products.

Substantiation of traditional use claims in the European Union

The 25 European Union member states have recently adopted a Traditional Herbal Medicine Directive (THMD) that is currently in an interim stage of implementation. This program establishes a system for an over-the-counter class of herbal products that are labeled with indications that are appropriate to traditional products and that require, among other things, that “the pharmacological effects or efficacy of the medicinal product are plausible on the basis of long-standing use and experience.”⁶ The THMD also requires that such products bear labeling to the effect that “the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.”⁷

⁶ Official Journal of the European Union. April 30, 2004. Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004, page L 136/87.

⁷ Ibid. Page L 136/89.

As noted above in discussing NHPs in Canada and herbal products sold in Australia, an important difference between the U.S. and E.U. regulation of herbal products is that dietary supplement in the United States are a subclass of foods, whereas goods marketed under the THMD in E.U. member states are a subclass of drugs. Nevertheless, issues related to substantiation of claims, especially in relation to claims based on traditional use, have much in common.

The Medicines and Healthcare products Regulatory Agency (MHRA) in the U.K. has published several documents to assist companies in coming into compliance with the THMD. In one of these⁸, MHRA states:

“...the Directive specifically makes clear there is no requirement to present data on tests and trials relating to efficacy. The required evidence of the medicine’s use for at least 30 years will often be indicative that there may well be at least some evidence as to the efficacy of the medicine. The labeling of the product will reflect this position with the wording: ‘traditional herbal medicinal product for use in specified indication(s) exclusively based upon long-standing use.’”

Thus, this new regulation implicitly accepts that a sufficiently long history of use – in this case 30 years – establishes a sufficient degree of substantiation for a claim that is consistent with an historical claim, so long as other factors such as dosage and composition are also consistent with traditional products. And as has been noted above, the kind of label qualifier discussed by FTC and recommended by the Commission on Dietary Supplement Labels and required in Canada and Australia has been adopted under this European regulatory program.

Since the emphasis under the THMD is on substantiating that a product has been marketed for 30 years, another MHRA document provides examples of the kinds of information that can be used to accomplish this. Numerous of the given examples may also be useful in providing direct evidence not only of presence in the marketplace, but of wide acceptance of the efficacy of the products. These include: Martindale: *List of Preparations*; German Rote List; Potter’s New Cylopaedia; text books; pharmacopoeia; and possibly others.

⁸ MHRA. July 2004. Directive on Traditional Herbal Medicinal Products – Answers to Some Frequently Asked Questions. page 13

Also, and similar to the process that is ongoing in Canada, the European Medicines Agency (EMA), which coordinates the evaluation and supervision of medicinal products throughout the E.U., is developing proposals for “core-data” for certain herbal ingredients. This work has been undertaken by EMA’s Working Party on Herbal Medicinal Products (HMPWP) and the resultant documents are identified as representing the views of the HMPWP and as having no legal force. The proposals for core-data, each of which includes appropriate “therapeutic indications” for products that meet prescribed quantitative and qualitative standards, are produced by reviewing and seeking expert consensus on scientific data, primarily from European Scientific Cooperative on Phytotherapy (ESCP) and World Health Organization (WHO) monographs.⁹

A list of current draft and final proposals for core-data for herbal ingredients are attached here as Appendix III. AHPA encourages FDA, consistent with the Agency’s statement that it “may accord some deference to” standards for substantiation developed by government agencies, to review these and to acknowledge that these documents may also have relevance for dietary supplement claims for products that conform to these proposals.

Estimates of collection of information provisions

FDA estimates that 2900 new dietary supplement products will come on to the market each year, and that 2001 of these will bear a structure/function claim. AHPA has no comment as to the accuracy of these estimates.

FDA further estimates that the 2001 new dietary supplement claims will be equally divided into three types of claims: “pre-existing widely established claims;” “pre-existing claims that are not widely established;” or “novel claims.” The only information provided by the Agency for this estimate is that the Agency has assumed it to be so. AHPA believes that such an assumption is arbitrary, but at the same time, AHPA has no additional information at this time that might be useful in establishing a better estimate.

⁹ Note that the ESCP and WHO monographs are also identified in the NHPD’s Sample Reference List: see Appendix II.

FDA also estimates that it will take only about an hour to assemble information needed to substantiate a dietary supplement claim that is pre-existing and widely established; and that it will take closer to 120 hours to assemble information needed to substantiate a dietary supplement claim that is either pre-existing and not widely established, or that is novel. AHPA has no comment at this time as to the accuracy of the estimate of 120 hours related to pre-existing and not widely established or novel claims. AHPA believes, however, that the estimate of one hour related to pre-existing and widely established claims is too low. Based on information received from AHPA members with responsibility to create and maintain files related to dietary supplement claims substantiation, a better estimate would be 30 to 40 hours.

AHPA acknowledges, however, that whether FDA has provided an accurate estimate of the time needed to assemble information needed to substantiate any dietary supplement claim, marketers of dietary supplements that wish to provide a structure/function claim on a dietary supplement product already bear the burden to have substantiation for the claim. FDA's Draft Guidance neither increases nor decreases that burden. Nevertheless, AHPA encourages the Agency to provide more accurate estimates to meet its obligation under the PRA, and to refrain from arbitrary assumptions in so doing.

Summary

As documented above, the FTC Advertising Guide, the Report of the Commission on Dietary Supplement Labels, and various international health regulatory authorities have recognized a category of traditional use claims based on evidence of traditional use. Surprisingly, the Agency's Draft Guidance appears to have rejected these approaches with just one dismissive comment. It is AHPA's position that the principles of traditional use substantiation addressed by the references cited herein should be examined by FDA and adopted.

It is a basic tenet of law that a claim for a product regulated under the Federal Food, Drug, and Cosmetic Act must be truthful and not misleading. It is AHPA's position that a traditional use claim, that is, a claim that a dietary supplement has

been traditionally used for a particular purpose, is properly substantiated by evidence of traditional use. Moreover, that evidence need only address the traditional use of the product, and not whether the benefit described or implied in the traditional use claim is achieved. It is AHPA's view that the public can be adequately informed by inclusion of a qualifying statement to the effect that traditional use is the sole basis for a traditional use claim. And this is in addition to the DSHEA disclaimer that accompanies such claims. Of course, if there were information contrary to the promise of the traditional use, that information would be required to be disclosed or the claim would be misleading for failure to reveal information material to the claim and the proposed use of the product.

AHPA has shown in these comments that in developing its Draft Guidance for substantiation of dietary supplement claims FDA has not acknowledged that evidence of traditional use of a dietary supplement ingredient may serve as competent and reliable evidence to substantiate claims that are consistent with traditional use and traditional formulations. Although FDA states that it has relied, in part, on the experience of the FTC and recommendations of the Commission on Dietary Supplement Labels, both FTC and the Commission acknowledge and describe the use of credible information related to traditional use to substantiate dietary supplement claims.

In addition, AHPA has provided important and significant information related to regulatory systems that exist in other countries for providing evidence for and substantiation of traditional use claims for herbal products. This information should not be considered exhaustive, but is instead representative of international regulatory systems that have been developed to allow information about traditional uses of products, and specifically herbal products, to serve as substantiation for contemporary claims that are consistent with traditional use.

Based on all of the above, AHPA strongly requests that FDA revise the Draft Guidance to specifically acknowledge that credible and authoritative information about traditional use does, in fact, represent competent and reliable evidence for claims, so long as the marketed product is in a form and dosage that is consistent with traditional use, the traditional use for which a claim is made is consistent with

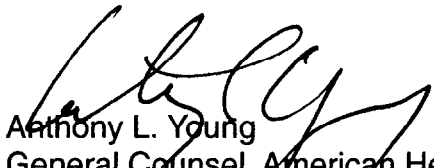
historical use, and there is not significant emerging information that contradicts traditional use references.

While AHPA encourages and expects the Agency to consider and respond to these comments and the information contained within them, AHPA's members are presently in the position of having a substantial portion of the traditional use claims that they make deemed not to be adequately substantiated under the principles of the Draft Guidance. Because the Draft Guidance either ignored or its authors were not informed of the Australian, Canadian and other international models, AHPA intends to advise its members that traditional use structure / function claims that meet the requirements of either the Canadian or the Australian systems can be considered to be substantiated and that AHPA will defend any member whose Canadian or Australian compliant products are proceeded against by FDA.

Respectfully submitted,



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Appendix I - NHPD (Canada) *Compendium of Monographs* (January 2005)

Table 1-A : Herbal monographs with oral use

Common name	Latin binomial	Plant part(s)
Alfalfa	<i>Medicago sativa</i>	aerial parts
Aloe	<i>Aloe vera</i>	latex of leaf cortex
Angelica	<i>Angelica archangelica</i>	root; large leaf; seed (fruit); rhizome
Astragalus	<i>Astragalus membranaceus</i>	Root
Avens	<i>Geum urbanum</i>	herb; root
Bilberry	<i>Vaccinium myrtillus</i>	fruit [†]
Birch	<i>Betula pendula</i>	Leaf
Black Cohosh	<i>Actaea racemosa</i>	root; rhizome
Black Horehound	<i>Ballota nigra</i>	aerial parts
Blessed Thistle	<i>Cnicus benedictus</i>	aerial parts [†]
Boldo	<i>Peumus boldus</i>	Leaf
Burdock	<i>Arctium lappa</i>	root [†]
Calendula	<i>Calendula officinalis</i>	flower [†]
California Poppy	<i>Eschscholzia californica</i>	aerial parts
Caraway	<i>Carum carvi</i>	Seed
Cascara Sagrada	<i>Frangula purshiana</i>	bark (aged 1 year)
Catnip	<i>Nepeta cataria</i>	aerial parts [†]
Cayenne	<i>Capsicum annuum</i>	fruit [†]
Cornflower	<i>Centaurea cyanus</i>	flower [†]
Cranberry	<i>Vaccinium macrocarpon</i>	Fruit
Dandelion	<i>Taraxacum officinale</i>	leaf; root
Devil's Claw	<i>Harpagophytum procumbens</i>	root (secondary tuber)
Echinacea angustifolia	<i>Echinacea angustifolia</i>	root; rhizome
Echinacea pallida	<i>Echinacea pallida</i>	root; rhizome
Echinacea purpurea	<i>Echinacea purpurea</i>	aerial parts [†] ; root [†]
Eleuthero	<i>Eleutherococcus senticosus</i>	Root
European Linden	<i>Tilia xeuropaea</i>	flower head
European Pennyroyal	<i>Mentha pulegium</i>	aerial parts (not concentrated oil for internal use) [†]
Evening Primrose	<i>Oenothera biennis</i>	seed oil

Appendix I (cont.)

Table 1-A : Herbal monographs with oral use (cont.)

Common name	Latin binomial	Plant part(s)
Fenugreek	<i>Trigonella foenum-graecum</i>	seed [‡]
Feverfew	<i>Tanacetum parthenium</i>	aerial parts; leaf
Figwort	<i>Scrophularia nodosa</i>	aerial parts [‡]
Flax	<i>Linum usitatissimum</i>	seed; seed oil
Frankincense	<i>Boswellia sacra</i>	gum resin from bark [‡]
Garlic	<i>Allium sativum</i>	bulb; oil from bulb
Gentian	<i>Gentiana lutea</i>	Root
Ginger	<i>Zingiber officinale</i>	root; rhizome
Globe Artichoke	<i>Cynara scolymus</i>	leaf; stem and root
Goldenseal	<i>Hydrastis canadensis</i>	root [‡] ; rhizome [‡]
Ground Ivy	<i>Glechoma hederacea</i>	aerial parts [‡]
Heal All	<i>Prunella vulgaris</i>	aerial parts [‡]
Hops	<i>Humulus lupulus</i>	Strobile
Horse Chestnut	<i>Aesculus hippocastanum</i>	Seed
Horseradish	<i>Armoracia rusticana</i>	root [‡]
Hyssop	<i>Hyssopus officinalis</i>	Herb
Juniper	<i>Juniperus communis</i>	fruit (berry)
Licorice	<i>Glycyrrhiza glabra</i>	root; stolon; rhizome
Linden	<i>Tilia cordata</i>	flower head [‡]
Lungwort	<i>Pulmonaria officinalis</i>	leaf [‡]
Milk Thistle	<i>Silybum marianum</i>	seed; fruit; leaf
Mugwort	<i>Artemisia vulgaris</i>	aerial parts [‡] ; root [‡]
Peppermint	<i>Mentha piperita</i>	leaf; oil
Rosemary	<i>Rosmarinus officinalis</i>	leaf [‡]
Saw Palmetto	<i>Serenoa repens</i>	Fruit
Scullcap	<i>Scutellaria lateriflora</i>	aerial parts
St. John's Wort	<i>Hypericum perforatum</i>	aerial parts [‡] ; flower [‡]
Stinging Nettle	<i>Urtica dioica</i>	aerial parts [‡] ; root [‡]
Thyme	<i>Thymus vulgaris</i>	leaf; flowering top; volatile oil [‡]
Turmeric	<i>Curcuma longa</i>	Rhizome
Valerian	<i>Valeriana officinalis</i>	root; rhizome
Witch Hazel	<i>Hamamelis virginiana</i>	leaf and bark (twig and branch) [‡]

‡ = for topical and oral use

Appendix I (cont.)

Table 1-B : Herbal monographs for topical use only

Common name	Latin binomial	Plant part(s)
Aloe	<i>Aloe vera</i>	leaf gel
Arnica	<i>Arnica Montana</i>	Flower
Hyssop	<i>Hyssopus officinalis</i>	volatile oil
Juniper	<i>Juniperus communis</i>	Oil
Thuja	<i>Thuja occidentalis</i>	leaf; branch tip
Thyme	<i>Thymus vulgaris</i>	volatile oil

Table 1-C : Non-herbal monographs

Arginine		
Biotin		
Calcium		
Chondroitin Sulphate		
Copper		
Folate		
Glucosamine		
Iodine		
Iron		
L-Tyrosine		
Lysine		
Melatonin		
Niacin		
Pantothenic Acid		
Riboflavin		
Selenium		
Vitamin A		
Vitamin B ₁		
Vitamin B ₆		
Vitamin B ₁₂		
Vitamin C		
Vitamin D		
Zinc		

Appendix II – NHPD (Canada) Sample Reference List

The following "Sample Reference List" is included as "Appendix 1" on pages 62-64 of the document, *Evidence For Safety And Efficacy Of Finished Natural Health Products*, published by the Natural Health Products Directorate (NHPD)), Canada. The document was accessed at http://www.hc-sc.gc.ca/hpfb-dgpsa/nhpd-dpsn/evidence_for_safety_efficacy_finished_nhp_e.pdf on January 6, 2005.

In other sections of this document this "Sample Reference List" was identified as follows:

- Applicants who make a traditional use claim must provide at least two independent references (i.e. references that do not cite the same source, or each other, as the main source of information regarding the traditional use) that support the conditions of use (see **Chapter 1.1**). The references must be authoritative and from a reputable source. Some examples of such references are provided in **Appendix 1** under the heading "References to Traditional Use" (page 11).
- The NHPD maintains a list of suggested references that are considered credible (see **Appendix 1**), which applicants may use to substantiate both the safety and efficacy of medicinal ingredients. However, this list is not exhaustive, but is a good starting point; other references must also be considered (page 23).
- The NHPD also maintains a list of sample references (see **Appendix 1**) that applicants may use to substantiate both the safety and efficacy of medicinal ingredients. This list is not exhaustive, but is a good starting point (page 16).
- This list is not exhaustive, but is a good starting point; other references must also be considered (see **Chapter 3.0**) as evidence to support the use of the natural health product.

SAMPLE REFERENCE LIST(as of July 2003)

References to Traditional Use

Bensky D, Barolet R. *Chinese Herbal Medicine: Formulas and Strategies*. Seattle (WA): Eastland Press; 1990.

Bensky D, Gamble A. *Chinese Herbal Medicine: Materia Medica*. Seattle (WA): Eastland Press; 1993 (2nd edition)

Hsu H-Y, Chen Y-P, Shen S-J, Hsu C-S, Chen C-C Chen, Chang H-C. *Oriental materia medica: a concise guide*. Long Beach (CA): Oriental Healing Arts Institute; 1986.

Marles RJ, Clavelle C, Monteleone L, Tays N, Burns D. *Aboriginal plant use in Canada's northwest boreal forest*. Vancouver (BC): UBC Press; 2000.

Millspaugh, Charles F. *American Medicinal Plants*. Dover (NY); 1974.
Moerman DE. *Native American ethnobotany*. Portland (OR): Timber Press Inc.; 1999.
Williamson, EM. *Major Herbs of Ayurvedic*. London (UK): Churchill Livingstone; 2002.

Appendix II (cont.)

Pharmacopoeia, Dispensatory

Bradley, P.R, editor. *British Herbal Compendium Vol. 1*. Bournemouth (UK): British Herbal Medicine Association; 1992.
British Herbal Pharmacopoeia. Great Britain (UK): British Herbal Medicine Association; 1996.
Felter HW, Lloyd JU. *King's American Dispensatory*. Sandy, OR: Eclectic Medical Publications;1983 (Volumes 1 and 2).
Pharmacopoeia of the People's Republic of China. English Edition. 2 volumes. Beijing: Chemical Industry Press; 1997.
The Homeopathic Pharmacopoeia of the United States. Washington DC: Homeopathic Pharmacopoeia Convention of the United States; Dec, 2000.
Upton R, editor. *American Herbal Pharmacopoeia and Therapeutic Compendium*. Santa Cruz (CA) (Monograph series).
USP 25-NF 20: *The United States Pharmacopeia & The National Formulary 20*. Rockville, MD: United States Pharmacopeial Convention Inc; 2002. (and supplements)
Willoughby MJ, Mills SY, compilers. *The British Herbal Pharmacopoeia*. Exeter, UK: A publication of the British Herbal Medicine Association; 1996.

Monographs

Blumenthal M, et al., editors. *Herbal Medicine: Expanded Commission E Monographs*. Boston (MA): Integrative Medicine Communications; 2000.
Blumenthal M, et al., editors. *The Complete German Commission E Monographs*. Boston (MA): Integrative Medicine Communications; 1998.
Blumenthal, M. and Riggins C.W. *Popular Herbs in the U.S. Market: Therapeutic Monographs*. Austin (TX): American Botanical Council;1997.
Monographs on the Medicinal Uses of Plant Drugs. Exeter (UK): A publication of the European Scientific Cooperative on Phytotherapy;1999.
WHO Monographs on Selected Medicinal Plants. Geneva (Switzerland): A World Health Organization publication;1999 (Volumes 1 and 2).

Reference Texts

Barnes J, Anderson LA, Phillison JD. *Herbal Medicines*. (2nd ed). London (UK): Pharmaceutical Press; 2002.
Bisset NG, editor. *Herbal Drugs and Phytopharmaceuticals*. Ann Arbor (MI): CRC Press; 1989.
Boon H, Smith M. *A Complete Natural Medicine Guide to the 50 Most Common Herbs: A Botanical Pharmacy*. Toronto (ON): Robert Rose Inc; 2003.
Brinker F. *Herb Contraindications & Drug Interactions*. (3rd ed). Sandy (OR): Eclectic Medical Publications; 2001.

Chandler F, editor. *Herbs: Everyday Reference for Health Professionals*. Ottawa (ON): Canadian Pharmacists Association and the Canadian Medical Association; 2000.
Huang, KC. *The Pharmacology of Chinese Herbs*. (2nd ed). Boca Raton (FL): CRC Press; 1999.
Jellin JM, Batz F, Hitchens K. *Pharmacist's Letter/ Prescriber's Letter Natural Medicines Comprehensive Database*. Stockton (CA): Therapeutic Research Faculty; 2003.
Leung AY, Foster S. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics*. (2nd ed). New York (NY): John Wiley & Sons, Inc; 1996.
McGuffin M, et al, editor. *Botanical Safety Handbook*. Boca Raton (FL): CRC Press; 1997
McGuffin M, Kartesz JF, Leung A Y, Tucker AO, editors. *Herbs of Commerce* (2nd ed). US: American Herbal Products Association; 2000.

Journals with a Focus on Peer-Reviewed Research Articles

Fitoterapia: The Journal for the Study of Medicinal Plants. Else vier Science Publishers, ISSN: 0367-326X
Journal of Ethnopharmacology. Elsevier Science Inc., Journal Information Center, 655 Avenue of the Americas, New York, NY 10010.
Pharmaceutical Biology (formerly *International Journal of Pharmacognosy*). Swets & Zeitlinger Publishers, P.O. Box 825, 2160 SZ Lisse, The Netherlands.
Phytomedicine. VCH Publishers Inc., 303 NW 12th Avenue, Deerfield Beach FL 33442-1705
Phytotherapy Research. Heyden & Son Ltd., Spectrum House, Hillview Gardens, London NW4 2JQ, United Kingdom;
Planta Medica. Georg Thieme Verlag, Stuttgart, Germany.

Appendix III – EMEA (EU) Proposals for Core-Data for Herbal Ingredients

Common name	Latin binomial	Plant part(s)
Calendula	<i>Calendula officinalis</i>	Flower
Devil's claw	<i>Harpagophytum procumbens</i>	secondary root tuber ‡
Hops	<i>Humulus lupulus</i>	strobile [‡]
Ispaghula	<i>Plantago ovata</i>	seed; seed husk
Linseed (Flax)	<i>Linum usitatissimum</i>	seed
Melissa (Lemon balm)	<i>Melissa officinalis</i>	leaf ‡
Nettle	<i>Urtica dioica</i> ; <i>U. urens</i>	leaf; root [‡]
Passionflower	<i>Passiflora incarnata</i>	herb ‡
Peppermint	<i>Mentha x piperita</i>	leaf; oil
Primula (Cowslip)	<i>Primula veris</i> ; <i>P. elatior</i>	root; rhizome
Psyllium	<i>Plantago psyllium</i> ; <i>P. indica</i>	seed
Thyme	<i>Thymus vulgaris</i> ; <i>T. zygis</i>	herb
Valerian	<i>Valeriana officinalis</i>	root; rhizome
Willow	<i>Salix purpurea</i> ; <i>S. daphnoides</i> ; <i>S. fragilis</i>	bark

‡ = Draft proposal

Docket No. 2004D-0466

AMERICAN HERBAL PRODUCTS ASSOCIATION

January 10, 2005

Attachment I

Australian Therapeutic Goods Administration Guidelines for Levels and Kinds
of Evidence to Support Indications and Claims

Guidelines for

Levels and Kinds of Evidence to Support

Indications and Claims

**For Non-Registerable Medicines,
including Complementary Medicines,
and other Listable Medicines**

Therapeutic Goods Administration

October 2001

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Complementary Medicines Evaluation Committee's Guide to Levels and Kinds of Evidence to Support Indications and Claims

EXECUTIVE SUMMARY

These guidelines have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listable medicines. In particular, they relate to complementary medicines, sunscreens and other Listable medicines. This Executive Summary provides a brief overview of how to support indications and claims for these medicines. Before using an indication or making a claim, you are strongly encouraged to read the entire document to ensure you are fully informed of all requirements.

Indications and claims can be based on evidence of traditional use of a substance or product, and/or on scientific evidence. Indications/claims and evidence are categorised as being 'general', 'medium' or 'high' level.

How to make indications/claims based on evidence of traditional use

To make an indication or claim based on evidence of traditional use, sponsors must first assess the level of the evidence supporting the claim.

If you hold one of the following four sources of evidence, you hold general level evidence.

1. TGA-approved Pharmacopoeia.
2. TGA-approved Monograph.
3. Three independent written histories of use in the classical or traditional medical literature.
4. Availability through any country's government public dispensaries for the indication claimed.

If you hold two of the above sources of evidence, you hold medium level evidence. Of course, the evidence, whether it is medium or general level, must support the indications or claims that you intend to make for your product.

If you hold general level evidence, you can make general level indications and claims. These include indications and claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

If you hold medium level evidence, you can make medium level indications and claims. These include the following kinds of indications and claims:

- Health enhancement;
- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; and
- Relief of symptoms of a named disease, disorder or condition.

All indications/claims based on evidence of traditional use must be worded to the effect that *"This (tradition) medicine has been traditionally used for (indication)"*. This applies to general and medium level indications/claims.

High level indications and claims are not permitted based on evidence of traditional use.

Similar principles apply to making indications and claims based on evidence of traditional use for homoeopathic and aromatherapy products.

How to make indications/claims based on scientific evidence

To make indications/claims based on scientific evidence sponsors must first assess the level of the evidence supporting the indication/claim.

Sponsors who hold general level evidence can make general level indications and claims. General level evidence includes:

1. Descriptive studies, case series or reports of relevant expert committees;
2. Texts, such as TGA-approved Pharmacopoeias or monographs; and
3. Other evidence based reference texts.

General level indications/claims include indications/claims relating to:

- Health maintenance, including nutritional support;
- Vitamin or mineral supplementation; and
- Relief of symptoms (not related to a named disease, disorder or condition).

The following kinds of evidence constitute medium level evidence:

1. Evidence obtained from well designed controlled trials without randomisation. In the case of a homoeopathic preparation, evidence from well-designed, controlled homoeopathic proving;
2. Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies; and
3. Evidence obtained from multiple time series with or without intervention, including within country and between country population studies.

(NOTE: In practice, the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.)

If you hold medium level evidence, you can make medium level indications and claims providing the evidence supports those indications/claims. Medium level indications/claims include indications/claims relating to:

- Health enhancement;
- Reduction of risk of a disease/disorder/condition;
- Reduction in frequency of a discrete event;
- Aids/assists in the management of a named symptom/disease/disorder/ condition; and
- Relief of symptoms of a named disease, disorder or condition.

Medium and general level indications and claims may only be made for minor, self-limiting conditions. Serious diseases or disorders may not be mentioned in medium or general level indications/claims.

High level indications/claims are indications or claims that refer to serious diseases or disorders or which relate to:

- Treatment, cure or management of any disease/disorder/condition;
- Prevention of any disease, disorder or condition;
- Treatment of a specific named vitamin or mineral deficiency diseases.

High level indications/claims require scientific evidence obtained from:

- a systematic review of all relevant randomised, controlled trials without significant variations in the directions and degrees of results; or
- at least one properly designed, randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. Advice should be sought from the TGA.

You can only make high level indications/claims for Registerable medicines. Listable medicines cannot carry high level indications and claims.

All indications/claims must be true, valid and not misleading, and should not lead to unsafe or inappropriate use of the product. Evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product/ingredient for which a claim is being made. Sponsors must hold evidence in line with these guidelines before claiming an intended use or indication for a product.

Complementary Medicines Evaluation Committee's Guide to Levels and Kinds of Evidence to Support Claims

INTRODUCTION

These guidelines have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listable medicines. In particular, they relate to complementary medicines, sunscreens and other Listable medicines. A glossary of terms used in these Guidelines is provided at Attachment 1.

The *Therapeutic Goods Act 1989* requires that at the time of Listing sponsors must hold the evidence to support indications and claims made in relation to Listable goods. All indications and claims made about therapeutic goods must be capable of substantiation – that is, evidence must be held by sponsors which demonstrates the indications and claims are true, valid and not misleading.

Listable goods are those products that meet the requirements of Schedule 4 of the Therapeutic Goods Regulations. Goods which do not meet the requirements of Schedule 4 and which are not exempt in Schedule 5, are Registrable. For guidance on the evidence requirements to support indications/claims for Registrable goods, these guidelines should be read in conjunction with other relevant guidelines published by the Therapeutic Goods Administration (TGA): for over the counter (OTC) medicines, the Australian Guidelines for the Registration of Drugs (volume 2); and for complementary medicines, the Australian Guidelines for Complementary Medicines (currently in preparation). Evidence to support indications/claims for Registrable goods must be submitted to the TGA for evaluation.

The therapeutic goods regulatory system

The regulation of complementary and other non-prescription medicines in Australia requires that they meet appropriate safety and quality standards. Registrable products are also evaluated for efficacy prior to being granted approval for their supply. These are products which contain active ingredients that are not exempt and/or which are not included in Schedule 4 of the Regulations, or that carry high level or otherwise Registrable indications/claims as defined in these guidelines¹. The sponsors of other products, Listed medicines, must hold appropriate evidence to support indications/claims for their products at the time of Listing. This evidence may be called in and evaluated by the TGA where a safety concern arises, indications/claims appear to be misleading, or in response to a complaint.

Almost all therapeutic goods approved for marketing in Australia carry one of two identifying numbers; these are the "AUST R" or the "AUST L" number on the front of the label. However, there are certain goods that are not required to carry these labels. These are "exempt" goods, and some medical devices. Registrable medical devices are required to carry an AUST R number; but declaration of an AUST L number on Listable devices is optional.

"AUST R" products are registered products that have been evaluated for safety, quality and efficacy. "AUST L" products are Listed non-prescription medicines and medical devices. Substances in Listable medicines are recognised as being of low risk, and are those that are

¹ Claims relating to the treatment, management, prevention or cure of diseases or disorders, or which in any other way refer to a serious disease, or treatment of specific named vitamin or mineral deficiency diseases.

included in Schedule 4 of the Regulations. Addition of new medicinal substances to Schedule 4 requires evaluation of their safety and quality. Prior to entering the market, Listable medicinal products are assessed by sponsors against defined standards including those for levels of evidence described in these guidelines. Listable devices are also recognised as being "low risk". All therapeutic goods are subject to on-going post-market surveillance.

The evaluation of medicines and medical devices for safety, quality, and where appropriate, efficacy, is undertaken by the TGA with advice from expert committees as required. Advice is provided by the Complementary Medicines Evaluation Committee (CMEC) for complementary medicines, by the Medicines Evaluation Committee (MEC) for other non-prescription medicines, by the Australian Drug Evaluation Committee (ADEC) for prescription medicines, and by the Therapeutic Devices Evaluation Committee (TDEC) for medical devices.

Where indications/claims are made in relation to therapeutic goods, the Therapeutic Goods Administration determines the standards these indications/claims must meet – a cornerstone of these standards is the evidence which must be held to support indications/claims. Sponsors of products carry the primary responsibility to ensure that indications/claims made about products are true, valid and not misleading in line with these standards, under the Listing system for medicines. However, should a question arise about the appropriateness of evidence supporting a indication/claim, the final evaluation of that evidence will be made by the TGA. Some Registrable goods may require special approval to advertise. The Therapeutic Goods Advertising Code Council is responsible for such recommendations (TGACC).

The TGACC is responsible for ensuring that the public interest is upheld for any advertisement of a therapeutic good. There are provisions relating to the advertising of non-prescription medicines and medical devices in the *Therapeutic Goods Act 1989* (the Act), the Therapeutic Goods Regulations (the Regulations), and in the Therapeutic Goods Advertising Code (TGAC) and its supporting guidelines.

LEVELS AND KINDS OF EVIDENCE TO SUPPORT CLAIMS

The three principles relating to indications and claims about therapeutic goods are:

1. before claiming an intended use or indication, sponsors must hold adequate evidence to support all claims they make about a product;
2. claims must be true, valid, and not misleading; and
3. claims should not lead to unsafe or inappropriate use of a product.

The kinds of evidence which may support claims

There are two types of evidence which may be used to support claims². These are:

- evidence based on traditional use of a substance or product; and
- scientific evidence.

How to use evidence of traditional use to support claims

Some 80% of the world's indigenous populations in developing countries depend on traditional systems of medicine and botanical medicines, and the use of traditional medicines

² Evidence held to support indications and claims must be in the English language, or be a Certified transcript translated from the native language.

is becoming more widespread in developed countries as well. Traditional medicines are based on an extensive history of use, often measured over thousands of years. This history provides an accumulated repository of systematic observation that underpins the use of these medicines.

Traditional use may infer community knowledge of the existence and application of a substance but does not necessarily carry with it any scientific assessment or scrutiny. For many products and substances there has been little quantifiable scientific research undertaken into their mode of action and effect. Evidence of traditional use may however be used to support claims for therapeutic goods. The following definition of 'traditional use' has been adopted by the CMEC for the purpose of these Guidelines.

Traditional use refers to documentary evidence that a substance has been used over three or more generations of recorded use for a specific health related or medicinal purpose.³

In assessing traditional use, the context of the claim is important. Most traditional forms of medicine are likely to use a mixture of substances, and certain behavioural rules promoting healthy diets and habits are likely to apply to them. In those cases, holistic principles are usually part of the therapy. Thus the theories, concepts and cultural context of the therapy need to be considered.

In forming a claim based on traditional use, products and substances which form part of traditional therapies should identify the therapy to which they belong or the paradigm in which the therapy has been traditionally used, as well as the product description/name and the symptom/indication/condition for which the product or substance is claimed to be beneficial. Traditional therapies are considered to include Traditional Chinese Medicine (TCM), traditional Ayurvedic medicine, traditional western herbal medicine, traditional homoeopathic medicine, aromatherapy and other indigenous medicines.

Modification of the classic formulations in Traditional Chinese Medicine (TCM) and Ayurvedic medicine must be based on the classical theory associated with the therapy and on traditional methods of preparation, in order for these products to make a traditional claim. For example, to meet the criteria for a traditional claim using evidence of traditional use, the overall formulation of a TCM needs to reflect the classical methods of combination. Traditional claims for combinations in Western Herbal formulations must be based on evidence linking the particular formulation (including methods of preparation) with traditional preparations, and must reflect the traditional knowledge about each individual herb in the product.

With respect to multigenerational use of homoeopathic medicines, it is recognised that homoeopathic medicine represents a special case where the manufacturing process of serial dilution is a major component of the tradition of use of the therapy. Providing that a new substance is prepared according to principles described in TGA-approved homoeopathic pharmacopoea (see Attachment 3), and satisfies safety requirements, claims may be assessed on an "evidence of traditional use" or "use in traditional practice" basis. Evidence of "traditional use" or "use in traditional practice" includes independent written histories of use in traditional or contemporary homoeopathic literature, multigenerational use, homoeopathic proving, records of clinical use and records of the set of symptoms provoked by a 'crude'

³ Where tradition of use has been recorded as an oral rather than written history, then evidence of such should be obtained from the appropriate practitioner or indigenous group(s), who maintain such a history.

substance. Claims made in relation to homoeopathic products must be consistent with the "homoeopathic picture" of the remedy or remedies on which the claim is based.

Substances or products which have been altered significantly in their constituent profile from the classical traditional medicine on which the claim is based, require scientific evidence in order to substantiate their claimed action.

Combinations of substances, some of which have a history of traditional use, and others which do not but are supported by scientific evidence, may make indications/claims based both on their traditional-use components and the scientific evidence, thus allowing a mixed claim. Should scientific evidence be contrary to the evidence based on traditional use, the claim used must reflect the truth, on balance of the evidence available. Where a claim in its entirety is supported by scientific evidence, and the sponsor wishes to mention that the ingredient or product has a tradition of use, the particular tradition from which the ingredient was derived need not be specified. For example:

"Echinacea helps support the immune system especially during the winter colds and flu season. This herb has been used traditionally for hundreds of years and now scientific evidence suggests that it may assist in supporting immune function"; or

"It has been known for hundreds of years that citrus fruits contained a substance which was important for good health. We now know that substance is vitamin C, and scientific studies have shown it is essential for maintaining healthy gums, blood vessels and connective tissue. Extra vitamin C may be important for individuals under stress".

It is not always possible to access the original reference which describes the traditional use, or use in traditional practice, for a product or substance. Indications and claims based on evidence of traditional use/ practice may be supported by contemporary literature reports of the original tradition, but they must be consistent with the wording specified for claims based on evidence of traditional use.

For multi-component Listable products, traditional claims can be based on the evidence of traditional use for the product itself, or on evidence for an individual component or components about which claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication. Where claims of synergy are made, the evidence of traditional use must support the synergistic effect. The dose of the ingredient or ingredients mentioned in the indication or claim must be consistent with the evidence, and the composition and preparation of the product must be consistent with the principles of the tradition about which the indication or claim is made.

Where multi-component products comprise active ingredients from different traditional therapies, the therapy from which the ingredient is derived, or the paradigm in which the therapy has been traditionally used, needs to be described if the ingredient is mentioned in a claim. For example, for a product formulated from *Panax ginseng*, *Bacopa monnieri* and soy-derived phosphatidyl serine, a claim might be made for the product, to the effect that "This product has been formulated from traditional and modern ingredients, to help support healthy memory". This could be entered on the Australian Register of Therapeutic Goods (ARTG) as the indication for the product.

However, if the sponsor wished to highlight the ingredients, they could use any or all of the following claims:

"*Panax ginseng* has been used for thousands of years in Traditional Chinese Medicine to tonify *qi*. It helps support memory in times of fatigue and convalescence."

"*Bacopa monnieri* has a tradition of use in Ayurvedic medicine for weakness of memory. It may help normal memory function."

"Soy-derived phosphatidyl serine has been shown in scientific studies help memory function in normal, healthy individuals."

How to use scientific evidence to support claims

In these guidelines scientific evidence refers to quantifiable data. Types of quantifiable scientific evidence include clinical trials in humans, epidemiological evidence, animal studies and other evidence of biological activity.

The greater the consistency of evidence across all these kinds, the greater the strength of the evidence. The strength of evidence will allow greater or lesser latitude in the nature of any claim and the wording that can truthfully be used.

The totality (balance and range), quality and relevance of the evidence to the claims are also important. The following descriptions of the meanings of totality, quality and relevance have been adapted from the United States Federal Trade Commission's (FTC's) "Business Guide for Dietary Supplement Industry Released by FTC Staff". (If readers are interested, the full version of the FTC's guidelines are available on the internet at the following website address: <http://www.ftc.gov/opa/1998/9811/dietary.htm>.)

Balance and range of the evidence

Studies cannot be evaluated in isolation of the surrounding context. The surrounding context of the scientific evidence is just as important as the internal validity of individual studies. Sponsors should consider all relevant research relating to the claimed benefit of their product and should not focus only on research that supports the effect, while discounting research that does not. A well-constructed literature search should normally be undertaken to help ensure that the general body of evidence on any particular topic is identified. (There are tutorials available on the internet on electronic database searching. Two such sites are:

http://www-library.uow.edu.au/InfoServ/USE/int_tut.htm; and

<http://www-library.uow.edu.au/EDT/index.html>.)

Balance and range of evidence may also be reflected in an authoritative review (these would normally be peer-reviewed and published).

Ideally, the studies relied on by a sponsor would be largely consistent with the surrounding body of evidence. Wide variation in outcomes of studies and inconsistent or conflicting results will raise serious questions about the adequacy of a sponsor's substantiation. Where there are inconsistencies in the evidence, it is important to examine whether there is a plausible explanation for those inconsistencies. In some instances, for example, the differences in results will be attributable to differences in dosage, the form of administration, the population tested, or other aspects of study methodology. Sponsors should assess how relevant each piece of research is to the specific claim they wish to make, and also consider the relative strengths and weaknesses of each. If a number of studies of different quality have

been conducted on a specific topic, sponsors should look first to the results of the studies with more reliable methodologies.

The Quality of the Evidence

In addition to the amount and type of evidence, quality of evidence is important. Where the claim is one that would require scientific support, the research should be conducted in a competent and reliable manner to yield meaningful results. The design, implementation, and results of each piece of research are important to assessing the adequacy of the substantiation.

There are some principles generally accepted in the scientific community to enhance the validity of test results. However, there is no single set protocol for how to conduct research. For example, a study that is carefully controlled, with blinding of subjects and researchers, is likely to yield more reliable results. A study of longer duration can provide better evidence that the claimed effect will persist and better evidence to resolve potential safety questions. Other aspects of the research results — such as evidence of a dose-response relationship (that is, the larger the dose, the greater the effect) or a recognised biological or chemical mechanism to explain the effect — are examples of factors that add weight to the findings.

Statistical significance of findings is also important. A study that fails to show a statistically significant difference between test and control group may indicate that the measured effects are merely the result of placebo effect or chance. The results should also translate into a meaningful, that is, clinically significant, benefit for consumers. Some results that are statistically significant may still be so small that they would mean only a trivial effect on consumer health.

The nature and quality of the written report of the research are also important. Research cannot be evaluated accurately on the basis of an abstract or an informal summary. However, other evidence can be considered, such as unpublished, proprietary research. The publication of a peer-reviewed study in a reputable journal indicates that the research has received some measure of scrutiny. At the same time, sponsors should not rely simply on the fact that research is published as proof of the efficacy of a substance or product. Research may yield results that are of sufficient interest to the scientific community to warrant publication, but publication does not necessarily mean that such research is conclusive evidence of a substance's or product's effect.

The Relevance of the Evidence to the Specific Claim

A common problem in substantiation of claims is that a sponsor has valid studies, but the studies do not support the claims intended to be made. Sponsors should make sure that the research on which they rely is not just internally valid, but also relevant to the specific product being promoted and to the specific benefit being claimed. Therefore, sponsors should ask questions such as: How does the dosage and formulation of the product compare to what was used in the study? Does the product contain additional ingredients that might alter the effect of the ingredient in the study? Is the product administered in the same manner as the ingredient used in the study? Has the product been tested for the same indications and claims as those proposed to be included in the ARTG? Does the study population reflect the characteristics and lifestyle of the population targeted by the product? If there are significant discrepancies between the research conditions and the real life use being promoted, sponsors need to evaluate whether it is appropriate to extrapolate from the research to the claimed effect.

In drafting indications and claims, the sponsor should take care to make sure that they match the underlying evidence support. Indications and claims that do not match the science, no matter how sound that science is, are likely to be unsubstantiated. Indications and claims should not exaggerate the extent, nature, or permanence of the effects achieved in a study, and should not suggest greater scientific certainty than actually exists. Although emerging science can sometimes be the basis for a carefully qualified claim, sponsors must make consumers aware of any significant limitations or inconsistencies in the scientific literature.

In line with these general principles for evaluating evidence, a framework for rating scientific evidence has been developed by the CMEC. This framework is adapted from the "Designation of Levels of Evidence" (National Health and Medical Research Council (NHMRC), 1999)⁴ and is consistent with international best practice. The rankings in the framework apply to evidence after it has been assessed with the degree of critical appraisal that would be applied by the TGA. The levels of the various kinds of scientific evidence are ranked by the CMEC as outlined in Table 1 on the next page.

All indications and claims based on scientific evidence require human studies. For those rare occasions where only non-human data exist, indications and claims may be allowed on a case-by-case basis. Supporting evidence may be used in conjunction with primary evidence to strengthen the wording of a claim.

In a claim based on scientific evidence, the recommended dosage of the product needs to be consistent with the evidence used to make the claim. The evidence must relate to the whole product or the same active constituent(s) with similar dosage regimen, dose form and route of administration to the product for which a claim is being made. When the evidence is based on an active constituent, qualification may be necessary according to how other constituents in the product may affect the activity of that constituent in the product.

A claim for a herb or herbal substance based on scientific evidence requires the herb, the part of the plant, the method of preparation and any processing, the equivalent dry weight and the dose of active or marker component to be consistent with the evidence used to make the claim. It is recognised that information about preparation and processing of ingredients could be confidential to the company providing the ingredient and therefore, not always be available to the sponsor. If this is the case, sponsors should provide evidence that the profile of the active ingredient(s) extracted using different manufacturing processes and solvents is not substantially different from the extract used in the clinical studies or other evidence used to support the claim.

⁴ NHMRC 1999. *A guide to the development, implementation and evaluation of clinical practice guidelines.*

Table 1: Levels of Scientific Evidence

Level	Type of Evidence
High	<p>Evidence obtained from a systematic review of all relevant randomised controlled trials, without significant variations in the directions or degrees of results.</p> <p>OR</p> <p>Evidence obtained from at least one properly designed randomised controlled (preferably multi-centre) double blind trial. It is preferable to have data from at least two trials independent of each other, but in some cases, one large well-conducted trial may suffice. (Advice should be sought from the TGA in such cases).</p>
Medium	<p>Evidence obtained from well designed controlled trials without randomisation. In the case of a homoeopathic preparation ⁵, evidence from well-designed, controlled homoeopathic proving.</p> <p>OR</p> <p>Evidence obtained from well designed analytical studies preferably from more than one centre or research group, including epidemiological cohort and case-control studies.</p> <p>OR</p> <p>Evidence obtained from multiple time series with or without intervention, including within country and between country population studies.</p> <p>NOTE: In practice the sources of most medium level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.</p>
General	<p>Descriptive studies, case series or reports of relevant expert committees. Texts, such as TGA-approved Pharmacopoeias or monographs (see Attachment 3), or other evidence based reference texts, may be included in this Level.</p>

Supporting evidence: Evidence derived from non-human data, such as *in vitro* studies and animal studies, and non-clinical studies such as biochemical, nutritional and microbiological studies does not stand alone and may only be used as supporting evidence.

Sponsors may wish to look at the Oxford University Centre for Evidence Based Medicine website for further qualification of types of scientific evidence. The website address is <http://cebm.jr2.ox.ac.uk/docs/levels.html>.

For multi-component Listable products, indications and claims can be based on the evidence for the product itself, or on evidence for an individual component or components about which indications and claims are made. In any instance where a claim links the presence of an ingredient to the product indication or claim, that ingredient must contribute to that indication or claim. Where claims of synergy are made, the evidence must support the synergistic effect. An example of how a claim for a multi-component product could be expressed as follows.

A product formulated as a "liver tonic" contains vitamins of the B-complex and *Silybum marianum*. Each vitamin is present at the Recommended Dietary Intake level, and the *Silybum marianum* is standardised to 70% silymarin. If the product had undergone clinical trial in humans and had been demonstrated to be efficacious, the claim could state to the

⁵ As defined in Regulation 2, *Therapeutic Goods Regulations*, 1990.

effect that this product has been formulated as a liver tonic and clinical trials had demonstrated it to be effective in maintaining a healthy liver and it may be beneficial in improving the function of the liver. However, if the efficacy of the product as a whole had not been evaluated, the product could carry indications/claims about the potential value of each of its ingredients. For example, *B-vitamins are important for a healthy liver, and studies have shown that silymarin is of benefit in helping the liver to recover from the toxic overload of everyday life.*

The types of indications and claims which can be made based on scientific evidence are described in the section of these Guidelines commencing on page 20. Using the system of categorisation described in that section, the claims in this example are general level (health maintenance) claims, and the actual evidence to support these claims for the active ingredients is found in ME Shils, JA Olson, M Shike and AC Ross, "Modern Nutrition in Health and Disease" 9th ed, Williams and Wilkins (1999), and the Commission E Monographs. Both are evidence-based reference texts, and the information in them is largely derived from medium or even high level evidence. Hence they support the general level claims made for this product.

What kinds of indications and claims does the evidence support?

As described earlier in these guidelines there are two types of evidence which can be used to support indications and claims for therapeutic goods. These are evidence based on traditional use of a product or substance, and scientific evidence.

Indications and claims based on evidence of traditional use

In Australia indications and claims which may be made about therapeutic goods using evidence of traditional use are categorised into two levels –medium and general – according to the relative strength of the claim. Medium level indications and claims are stronger but more evidence is required to support them. This general approach is summarised in Table 2. Specific approaches have been developed for homoeopathic and aromatherapy products and these approaches are summarised in Tables 3 and 4 respectively. A summary of the definitions of the types of claims is provided at Attachment 2 to these guidelines.

Table 2: Levels and types of claims and the evidence required to support them – based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim ²	Evidence required to support claim
MEDIUM	<ul style="list-style-type: none"> ▪ Health enhancement¹ ▪ Reduction of risk of a disease/disorder/condition. ▪ Reduction in frequency of a discrete event. ▪ Aids/assists in the management of a named symptom/disease/disorder/condition.⁶ ▪ Relief of symptoms of a named disease/disorder/condition.⁶ 	This (tradition) medicine has been used for (indication) ^{3,5} .	<p>Primary evidence: <i>Two of the following four sources that demonstrate adequate support for the indications claimed:</i></p> <ol style="list-style-type: none"> 1. TGA-approved Pharmacopoeia.⁷ 2. TGA-approved Monograph.⁷ 3. Three independent written histories of use in the classical or traditional medical literature⁴. 4. Availability through any country's government public dispensaries for the indication claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- ¹Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- ²Or words to this effect
- ³Where scientific evidence is available to support the entire claim the tradition from which the medicine originated need not be specified.
- ⁴In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support claims.
- ⁵Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example “Shen” not “Kidney” in TCM.
- ⁶All indications/claims relating to symptoms must be accompanied by the advice “If symptoms persist consult your healthcare practitioner” or words to that effect.
- ⁷See Attachment 3.

Table 2 (cont'd) Levels and types of claims and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim ¹	Evidence required to support claim
GENERAL	<ul style="list-style-type: none"> Health maintenance, including for example indications/claims relating to nutritional support. Relief of symptoms (not referring to a named disease, disorder or condition)². Claims for traditional syndromes and actions³. 	This (tradition) medicine has been traditionally used for (indication) ³ .	<p>Primary evidence: One of the following four sources that demonstrates adequate support for the indications claimed:</p> <ol style="list-style-type: none"> 1. TGA-approved Pharmacopoeia.⁵ 2. TGA-approved Monograph.⁵ 3. Three independent written histories of use in the classical or traditional medical literature⁴. 4. Availability through any country's government public dispensaries for the indication claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- ¹Or words to this effect.
- ²All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- ³Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations, for example "Shen" not "Kidney" in TCM.
- ⁴In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support indications/claims.
- ⁵See Attachment 3.

Table 3: Levels and types of claims for homoeopathy and the evidence required to support them - based on evidence of traditional use or evidence of traditional practice

Level of claim	Type of claim	Wording of Homoeopathic Claim ¹	Evidence required to support homoeopathic claim
MEDIUM	<ul style="list-style-type: none"> Health enhancement². Aids/assists in the management of a symptom complex of a named symptom/disease, disorder or condition.³ Relief of symptoms of a named disease, disorder or condition³. 	This homoeopathic medicine has been traditionally used for (indication) ⁵ , or, This homoeopathic medicine has been prepared by traditional methods for (indication) ^{5,6} .	<p>Primary evidence: Two of the following three sources that demonstrate adequate support for the indications claimed:</p> <ol style="list-style-type: none"> Well-designed homoeopathic proving of the substance(s) or a TGA-approved⁷ Homoeopathic Materia Medica and a Homoeopathic Repertory. Three independent written histories of use in the traditional or contemporary homoeopathic literature⁴. Availability through any country's government public dispensaries for the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.

Notes:

- ¹Or words to this effect.
- ²Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- ³All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- ⁴In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated.
- ⁵Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations..
- ⁶Where scientific evidence is available for this claim the tradition from which the medicine originated need not be specified.
- ⁷See Attachment 3.

Table 3: Levels and types of claims for homoeopathy and the evidence required to support them - based on evidence of traditional use or evidence of traditional practice (cont'd)

Level of claim	Type of claim	Wording of Homoeopathic Claim ¹	Evidence required to support homoeopathic claim
GENERAL	<ul style="list-style-type: none"> Health maintenance, including for example indications/claims relating to nutritional support. Relief of symptoms (not referring to a named disease, disorder or condition)². Claims for traditional syndromes and actions⁴. 	This homoeopathic medicine has been traditionally used for (indication) ⁴ , or, This homoeopathic medicine has been prepared by traditional methods for (indication) ⁴ .	Three independent written histories of use ³ in the traditional or contemporary homoeopathic literature; or homoeopathic provings supporting the indications claimed.

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence. In addition, records of the set of symptoms provoked by the crude substance may be used. This evidence may only be used in conjunction with the homoeopathic evidence referred to above.

Notes:

- ¹Or words to this effect.
- ²All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- ³In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated.
- ⁴Claims making reference to traditional (indigenous) physiological terms should, where appropriate, use the original terms to avoid potentially confusing or inaccurate translations..

Table 4: Levels and types of claims for aromatherapy and the evidence required to support them - based on evidence of traditional use

Level of claim	Type of claim	Wording of Claim ¹	Evidence required to support claim
MEDIUM	<ul style="list-style-type: none"> Health enhancement². Reduction in frequency of a discrete event. Aids/assists in the management of a named symptom/disease/disorder/ condition.³ Relief of symptoms of a named disease, disorder or condition³. 	This essential oil has been traditionally used for (indication). ⁴	<p>Primary evidence: Two of the following three sources that demonstrate adequate support for the indications claimed:</p> <ol style="list-style-type: none"> 1. TGA-approved Pharmacopoeia.⁶ TGA-approved Monograph.⁶ 2. Three independent written histories of use in the traditional aromatherapy literature.⁵ 3. Availability through any country's government public dispensaries for the indication claimed.
GENERAL	<ul style="list-style-type: none"> Health maintenance Relief of symptoms (not referring to a named disease, disorder or condition)³. 	This essential oil has been traditionally used for (indication).	Three independent written histories of use in the traditional aromatherapy literature supporting the indications claimed ⁵ .

Supporting evidence: Evidence commonly referred to in appropriate prescribed teaching textbooks used in university training of healthcare professionals does not stand alone and may only be used as supporting evidence.

Notes:

- ¹Or words to this effect.
- ²Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- ³All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- ⁴Where scientific evidence is available for this claim the tradition from which the medicine originated need not be specified.
- ⁵In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use was authenticated. Modern texts which accurately report the classical or traditional literature may be used to support indications/claims.
- ⁶See Attachment 3.

The following information and examples of how to use evidence of traditional use to support indications/claims is an adaptation of the information in the US FTC guidelines, and has been incorporated into these Australian Guidelines.

Indications and claims based on historical or traditional use should be substantiated by confirming scientific evidence, or should be presented in such a way that consumers

understand that the sole basis for the claim is a history of use of the product for a particular purpose. A number of products, particularly herbal products, have a long history of use as traditional medicines to treat certain conditions or symptoms.

Indications and claims based solely on traditional use should be presented carefully to avoid the implication that the product has been scientifically evaluated for efficacy. The degree of qualification necessary to communicate the absence of scientific substantiation for a traditional use claim will depend in large part on consumer understanding of this category of products. As consumer awareness of and experience with "traditional use" supplements evolve, the extent and type of qualification necessary is also likely to change.

There are some situations, however, where traditional use evidence alone will be inadequate to substantiate a claim, even if that claim is carefully qualified to convey the limited nature of the support. In determining the level of substantiation necessary to substantiate a claim, the consequences of a false claim must be taken into consideration. Indications and claims that, if unfounded, could present a substantial risk to consumer health or safety will be held to a higher level of scientific proof.

Sponsors should also make sure that they can support the extent and manner of historical use and be careful not to overstate such use. Sponsors should make sure that the product to be marketed is consistent with the product as traditionally administered. If there are significant differences between the traditional use product and the marketed product, in the form of administration, the formulation of ingredients, the dose, or the indication for which the product has been used, a "traditional use" claim may not be appropriate.

Example 1: The sponsor of a herbal supplement makes the claim, "Ancient folklore remedy used for centuries by Native Americans to aid digestion." The statement about traditional use is accurate and the supplement product is consistent with the formulation of the product as traditionally used. However, if this statement was used in a context which suggested that scientific evidence demonstrates efficacy where no such evidence exists, this would be misleading and, therefore, unacceptable.

Example 2: A sponsor wants to market a herbal product that has been used in the same formulation in China as a tonic for improving mental functions. The sponsor prepares the product in a manner consistent with Chinese preparation methods. The claims are, "Traditional Chinese Medicine — Used for Thousands of Years to Bring Mental Clarity and Improve Memory." The product label also contains language that clearly conveys that the efficacy of the product has not been confirmed by research, and that traditional use does not establish that the product will achieve the claimed results. The label is likely to adequately convey the limited nature of support for the claim.

Indications and claims based on scientific evidence

There are various types of indications and claims based on scientific evidence that can be made; they are generally categorised according to the type of information they convey. Additionally, claims can be ranked in relation to the relative strength of the claim and their likely impact on consumers. These rankings provide a basis for the level of scientific evidence which may be required to support each type of claim. In Australia, indications and

claims which may be made about therapeutic goods are categorised into three levels - high, medium and general. Different levels of evidence are required to support each level of claim. Within these three levels there are several different types of indications and claims which may be made. For simplicity, this approach can be summarised as shown in Table 5. A summary of the definitions of the types of claims is provided at Attachment 2 to these guidelines.

There is a wide variety of references, research papers and texts which may be used as sources of evidence to support these indications and claims. Sponsors should make sure that the research on which they rely is relevant to the specific product being promoted and to the specific benefit being claimed. Further guidance for Registrable products is available in the Australian Guidelines for the Registration of Drugs (volume 2) for OTC products, and for complementary medicines, the Australian Guidelines for Complementary Medicines (currently in preparation).

Table 5: Levels and types of claims and the evidence required to support them - based on scientific evidence

Level of claim	Type of claim	Evidence required to support claim
HIGH¹	<ul style="list-style-type: none"> ▪ Treats/cures/manages any disease/disorder/condition. ▪ Prevention of any disease, disorder or condition. ▪ Treatment of specific named vitamin or mineral deficiency diseases. 	High level. Registration only – evaluated by the CMEC, MEC or ADEC.
MEDIUM	<ul style="list-style-type: none"> ▪ Health enhancement². ▪ Reduction of risk of a disease/disorder/condition. ▪ Reduction in frequency of a discrete event. ▪ Aids/assists in the management of a named symptom/disease/disorder/condition.³ ▪ Relief of symptoms of a named disease, disorder or condition³. 	Medium level. Sponsor must hold the evidence for Listable goods.
GENERAL	<ul style="list-style-type: none"> ▪ Health maintenance, including nutritional support. ▪ Vitamin or mineral supplementation⁴. ▪ Relief of symptoms (not related to a named disease, disorder or condition)³. 	General level. Sponsor must hold the evidence for Listable goods.

Notes:

- ¹There are some specific exemptions to this table which are not considered to be high level claims. These are listed on the TGA website at www.health.gov.au/tga.
- ²Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.
- ³All indications/claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner" or words to that effect.
- ⁴Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Where vitamins or minerals are the subject of other kinds of

claims, the dose must be consistent with the evidence to support the claim being made. Indications/claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

REGISTRABLE DISEASES LIST

There is a list of diseases/disorders/conditions about which indications/claims may be made only after evaluation of the product and the claim(s) through Registration of the product. The list refers to serious diseases/disorders/conditions and it applies to indications and claims based on evidence of traditional use, as well as to those based on scientific evidence. The list is known as the 'Registrable disease' list and it applies to medicines but not devices. Decisions made with respect to the Registration of medical devices are based on a different set of categorisations and guidelines.

The definition of a serious disease, disorder or condition is one for which there is a substantial body of medical opinion that the disease (disorder or condition) cannot or should not be diagnosed or treated except under medical advice.

Indications/claims for Registrable diseases may be made under certain circumstances, but only after the safety, quality and efficacy of the product and the claim(s) have been evaluated by the CMEC or other relevant evaluation committee. Where a sponsor seeks to mention a Registrable disease in what would otherwise have been categorised as a medium or general level claim, that claim would become Registrable and the product would require Registration (that is, evaluation by the TGA with the advice of the CMEC, MEC, or ADEC). The 'Registrable disease' list is shown in Table 6.

Table 6: The Registrable disease list (for medicines)

Disease/disorder/condition/action – serious manifestation of	
Abortifacient action.	Infectious diseases, including sexually transmitted diseases.
Cardiovascular diseases.	Insomnia, persistent.
Dental and periodontal disease.	Mental diseases, ailments or defects, including substance abuse.
Diseases of joint, bone, collagen, and rheumatic disease.	Metabolic disorders.
Diseases of the eye or ear likely to lead to severe impairment, blindness or deafness.	Musculoskeletal diseases.
Diseases of the liver, biliary system or pancreas.	Neoplastic disease (all cancers).
Endocrine diseases and conditions, including diabetes and prostatic disease.	Nervous system diseases.
Gastrointestinal diseases.	Renal diseases, diseases of the genito-urinary tract.
Haematological disorders and diseases.	Respiratory diseases.
Immune disorders and diseases.	Skin diseases.
Other	
Immunisation	Poisoning, venomous bites and stings – treatment of.

There are some exceptions to the Registrable disease list, whereby diseases, disorders or conditions which would normally require Registration may be mentioned in indications and claims on Listed medicines. These exceptions will be listed in the new version of the Electronic Lodgement Facility (ELF3) coded indications and are provided in hard copy

format on the TGA website at www.health.gov.au/tga. Where there is no suitable coded indication in ELFversion 2, these new indications and claims may be entered as free text in item 27.

IN CONCLUSION

Further advice on the whole or any part of these Guidelines can be sought from the TGA, the major industry associations, and from regulatory affairs consultants.

GLOSSARY OF TERMS USED IN THESE GUIDELINES

Blinding

Blinding (also called masking) is a procedure in which one or more parties in a clinical trial are kept unaware of the treatment assignment(s). Blinding is used so that neither the patients' nor staff's expectations about the medicine or treatment under investigation can influence the outcome.

Case study

In depth description of the factors related to a disease, disorder or condition in a specific individual (CHC).

Case-control study

A study that starts with identification of people with the disease, disorder or condition of interest (the cases) and a suitable control group without the disease or outcome (the controls). The relationship of an attribute (medicine, treatment, exposure or risk factor) to the outcome of interest is examined by comparing the frequency or level of the attribute in the cases and in the controls. For example, to determine whether thalidomide caused birth defects, a group of children with birth defects (cases) could be compared to a group of children without birth defects (controls). The groups would then be compared with respect to the proportion exposed to thalidomide through their mothers taking the tablets. Case-control studies are sometimes described as being retrospective as they are always performed looking back in time.

Clinical significance

The quality of a study's outcome that convinces physicians to modify or maintain their current practice of medicine. The assessment of clinical significance is usually based on the size of the effect observed, the quality of the study that yielded the data, and the probability that the effect is a true one. Clinical significance is not the same as statistical significance; a finding in a study may demonstrate a statistical difference in an attribute under review but this may have no impact clinically.

Clinical trial/clinical study (synonym: intervention study)

A planned study in humans designed to discover or verify:

- the clinical, pharmacological and/or other pharmacodynamic effects of a medicine or treatment; and/or
- to identify any adverse reactions to a medicine or treatment; and/or
- to study absorption, distribution, metabolism and excretion of a medicine or treatment, with the object of ascertaining its safety and/or efficacy.

Clinical trials of experimental medicines proceed through four phases:

- In Phase I, researchers test a new medicine or treatment in a small group of normal, healthy volunteers (20-80) for the first time to evaluate its safety, determine a safe dosage range and identify side effects.
- In Phase II, the study drug or treatment is given to a larger group of people with the disease/disorder of interest (100-300) to see if it is effective and to further evaluate its safety.

- In Phase III studies, the study drug or treatment is given to large groups of people with the disease/disorder of interest (1,000 – 3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatment and collect information that will allow the drug or treatment to be used safely.
- Phase IV studies are done after the medicine or treatment has been marketed following regulatory approval. These studies continue testing the study drug or treatment to collect information about their effect in various populations and any side effects associated with long-term use.

Cochrane Review

A Cochrane Review is a systematic, up-to-date summary of reliable evidence of the benefits and risks of healthcare. For a review to be called a "Cochrane Review" it must be in the Parent database maintained by the Cochrane Collaboration. The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of healthcare interventions.

Cohort study (synonyms: follow-up, incidence, longitudinal, prospective study)

An observational study in which a defined group of people (the cohort) is followed over time. The outcomes of people in subsets of this cohort are compared, (e.g. to examine people who were exposed or not exposed, or exposed at different levels, to a particular intervention or other factor of interest). A cohort can be assembled in the present and followed into the future (this would be a prospective study or a "concurrent cohort study"), or the cohort could be identified from past records and followed from the time of those records to the present (this would be a retrospective study or a "historical cohort study"). Because random allocation is not used, matching or statistical adjustment at the analysis stage must be used to minimise the influence of factors other than the intervention or factor of interest.

Condition: A simplified description for a disorder, which is a derangement or abnormality of function.

Control

In clinical trials comparing two or more interventions, a control is a person in the comparison group that does not receive the medicine or treatment under evaluation. Instead that person receives a *placebo*, no intervention, usual care or another form of care. In case-control studies, a control is a person in the comparison group without the disease or outcome of interest.

In statistics, to control means to adjust for or take into account extraneous influences or observations.

Controlled clinical trial

Refers to a study that compares one or more intervention groups to one or more comparison (control) groups. Whilst not all controlled studies are randomised, all randomised trials are controlled.

Crossover trial

This is a research design in which subjects receive a number of treatments in sequence. Generally, this means that all subjects have an equal chance during the trial of experiencing both treatment and placebo dosages without direct knowledge, instead of either placebo or the treatment. Subjects may be transferred directly from one treatment to another or may have a

washout period in between test treatments. This type of trial can be randomised so that all subjects don't get the alternative treatments in the same order.

Disease: Any deviation or interruption of the normal structure or function of any part, organ or system (or combination thereof) of the body that is manifested by a characteristic set of symptoms and signs and whose aetiology, pathology and prognosis may be known or unknown.

Disorder: a derangement or abnormality of function.

Dosage form

The pharmaceutical form in which a product is presented for therapeutic administration (e.g. tablet, cream).

Dosage regimen

The number of doses per given time period, the time that elapses between doses or the quantity of a medicine that is given at each specific time of dosing.

Double blind

Neither the participants in a trial nor the investigators (outcome assessors) are aware of which intervention the participants are given during the course of the trial.

Efficacy

A relative concept referring to the ability of a medicine or treatment to achieve a beneficial clinical effect. This may be measured or evaluated using objective or subjective parameters.

Endpoint

An indicator measured in a patient or biological sample to assess safety, efficacy or another trial objective. Also defined as the final trial objective by some authors.

Epidemiology

The study of the distribution and determinants of health-related states or events in specified populations.

Evidence-based textbook

A textbook based on a critical and systematic review of published data, not simply on the opinions of the author(s).

Good clinical practice

A standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

Placebo

An inactive substance or treatment that supposedly has no treatment value. It is given to participants in clinical trials as a control against which to compare the effects of the test substance. In practice, placebos may also have positive or negative effects on trial participants.

Population studies

Investigations of a disease or condition using subjects from a defined population. A population is a closely distributed grouping from a single community that is characterised by both genetic and cultural continuity through several generations.

Protocol

All clinical trials are based on a protocol, which describes who may participate in a trial, the length of a trial and the schedule of tests, procedures, medications and dosages.

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomised controlled trial (RCT)

An experiment in which investigators randomly allocate eligible people into intervention groups to receive or not to receive one or more interventions that are being compared. The results are assessed by comparing outcomes in the treatment and control groups.

Sign: any objective evidence of a disease, that is, such evidence as is perceptible to the examining physician, as opposed to the subjective sensations (symptoms) of the patient.

Single blind

A clinical trial where the participants are unaware of the whether they are receiving the placebo or active medicine or treatment.

Site

This refers to the place where a clinical trial is conducted. When a clinical trial is conducted at more than one site, but using the same protocol, it is referred to as a multi-site or multi-centre trial.

Statistical significance

The probability that an event or difference is real or occurred by chance alone. It does not indicate whether the difference is small or large, important or trivial. The level of statistical significance depends on the number of patients studied or observations made, as well as the magnitude of difference observed. Statistical significance observed in a clinical trial does not necessarily imply clinical significance.

Subject/trial subject

An individual who participates in a clinical trial, either as a recipient of the medicine or treatment, or as a control.

Syndrome: A set of symptoms which occur together; a symptom complex.

Symptom: any subjective evidence of disease or of a patient's condition, that is, such evidence as perceived by the patient.

Systematic review

An analysis of a large number of clinical trials (sometimes known as a 'meta-analysis') aimed at looking for an overall pattern in the trial results. Cochrane Reviews are examples of such systematic reviews. In a systematic analysis only those trials which meet a number of pre-set

conditions in relation to research design (e.g. sample size, randomisation) are included in the final meta-analysis.

Therapeutic good

The *Therapeutic Goods Act 1989* defines a therapeutic good as follows:

“therapeutic goods means goods:

- (a) that are represented in any way to be, or that are, whether because of the way in which the goods are presented or for any other reason, likely to be taken to be:
 - (i) for therapeutic use; or
 - (ii) for use as an ingredient or component in the manufacture of therapeutic goods; or
 - (iii) for use as a container or part of a container for goods of the kind referred to in subparagraph (i) or (ii); or
- (b) included in a class of goods the sole or principal use of which is, or ordinarily is, a therapeutic use or a use of a kind referred to in subparagraph (a)(ii) or (iii); and includes goods declared to be therapeutic goods under an order in force under section 7, but does not include:
 - (c) goods declared not to be therapeutic goods under an order in force under section 7; or
 - (d) goods in respect of which such an order is in force, being an order that declares the goods not to be therapeutic goods when used, advertised, or presented for supply in the way specified in the order where the goods are used, advertised, or presented for supply in that way; or
 - (e) goods for which there is a prescribed standard in the Australia New Zealand Food Standards Code as defined in subsection 3(1) of the *Australia New Zealand Food Authority Act 1991*; or
 - (f) goods which, in Australia or New Zealand, have a tradition of use as foods for humans in the form in which they are presented.”

Therapeutic use

The *Therapeutic Goods Act 1989* defines therapeutic use as follows:

“*therapeutic use* means use in or in connection with:

- (a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; or
- (b) influencing, inhibiting or modifying a physiological process in persons or animals; or
- (c) testing the susceptibility of persons or animals to a disease or ailment; or
- (d) influencing, controlling or preventing conception in persons; or
- (e) testing for pregnancy in persons; or
- (f) the replacement or modification of parts of the anatomy in persons or animals.”

Washout period

The stage in a cross-over trial where treatment is withdrawn before a second treatment is given. This is usually necessary to counteract the possibility that the first substance can continue to affect the subject for some time after it is withdrawn.

Acknowledgements:

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Additional information was obtained from:

- Australian Guidelines for the Registration of Drugs. Volume 1. Prescription Medicines. Canberra: Therapeutic Goods Administration
- Complementary Healthcare Council of Australia
- Miller-Keane Encyclopaedia and Dictionary of Medicine, Nursing & Allied Health. 6th Edition. Philadelphia: Saunders. 1997
- Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95). TGA, DSEB (2000)
- Spilker B. 1996. Guide to clinical trials. Philadelphia: Lippincott-Raven Publishers
- US National Institute of Health, Clinical Trials service (www.clinicaltrials.gov/)

DEFINITIONS – TYPES OF CLAIMS

Aids/Assists claims – a claim which describes how a product or substance may aid/assist in the management of a named symptom/disease or disorder.

Discrete events claims – a claim which refers to the ability of a product or substance to reduce the frequency of a discrete event such as migraine.

Disease management claim – a claim that a product or substance can treat, cure or manage a particular disease, disorder, condition or ailment.

Preventive claim – a claim which relates to preventing a particular disease, disorder, condition, symptom or ailment.

Risk reduction claim – a claim which relates to reducing the risk of a particular disease, disorder, condition, symptom or ailment.

Health enhancement claim – health maintenance claims which relate to health enhancement for normal healthy people, such as improving, promoting, enhancing or optimising (or words to that effect) body organs or systems.

Health maintenance claim – a claim which refers to an effect a product or substance may have in maintaining health (or words to that effect), but not including health enhancement or prevention claims. Health maintenance claims may also relate to the normal physiological consequences for good health associated with a product or substance, or to the provision of nutritional support and to the use of the terms, cleansing, detoxification and tonic.

Symptom claim – a claim which relates specifically to the temporary relief of a particular symptom. All symptom claims must be accompanied by the statement “If symptoms persist consult your healthcare practitioner” or words to that effect.

Claims relating to specific named vitamin or mineral deficiency diseases – claims which refer to the name of a vitamin or mineral and a recognised deficiency disease.

Claims relating to vitamin or mineral supplementation – claims that refer to supplemental intakes of the vitamin or mineral. Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. The RDI in this context refers to the Australian RDI. If there is no Australian RDI for a vitamin or mineral, an RDI from another country may be used. Vitamin and mineral claims of any kind should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10% of the RDI, unless there is evidence to support a therapeutic effect below this level.

TGA-APPROVED TEXTS

MONOGRAPHS

- Blumenthal M et al (eds) (2000) *Herbal Medicine - Expanded Commission E monographs*, American Botanical Council, Austin, Texas. (Note: Commission E monographs may constitute medium level evidence. However, only positive monographs can be used as positive evidence to support claims.)
- European Scientific Co-operative on Phytotherapy (ESCOP) series (1996) *Monographs on the Medicinal Uses of Plant Drugs*, ESCOP, Exeter.
- World Health Organization (WHO) (1999) *Monographs on Selected Medicinal Plants*, Volume 1, WHO, Geneva.
- Yu HC, Kosuna K and Haga M (Eds) (1997) *Perilla: the Genus Perilla*, Harwood Academic Publishers, Amsterdam.

PHARMACOPOEAS

- *British Herbal Pharmacopoeia* (1996) 4th edition, British Herbal Medicines Association, West Yorks, England.
- *European Pharmacopoeia* (1997) 3rd edition, Council of Europe, Strasbourg.
- *Martindale: the Extra Pharmacopoeia* 91996) 31st edition, Pharmaceutical Press, London.
- *The British Pharmaceutical Codex*, Pharmaceutical Press, London.
- *The British Pharmacopoeia* (1998), Her Majesty's Stationery Office, London.
- *The United States Pharmacopoeia and National Formulary USP24/NF19* (2000) USP Convention Inc, Rockville, Maryland.
- *Pharmacopoeia of the People's Republic of China* (1997), Vol 1.

Other TGA-approved pharmacopoeias on advice from expert committees.

NOTE add in UK homoeopathic pharmacopoeia.

MATERIA MEDICA AND REPERTORY

- Boericke W (1927) *Pocket Manual of Homoeopathic Materia Medica, comprising the characteristic and guiding symptoms of all remedies (clinical and pathogenetic)*, Boericke and Runyon Inc, New York, USA.
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- Reckeweg HH (1991) *Materia Medica*, volume 1, Aurelia Verlag, Baden Baden, Germany, ISBN 3-922907-16-4.

- Vermeulen F (1997) *Concordant Materia Medica*, 2nd edition, Emryss bv, Haarlem, The Netherlands.
- Vermeulen F () *Synoptic Materia Medica*, volumes 1 and 2, further details needed.